NATIONAL INSTITUTES OF HEALTH
POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF
HUMAN SOMATIC-CELL GENE THERAPY PROTOCOLS

HUMAN GENE THERAPY SUBCOMMITTEE
NIH RECOMBINANT DNA ADVISORY COMMITTEE

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Adopted by
Recombinant DNA Advisory Committee
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POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN

SOMATIC-CELL GENE THERAPY PROTOCOLS

Applicability - These "Points to Consider" apply only to research conducted at or sponsored by an institution that receives any support for recombinant DNA research from the National Institutes of Health (NIH). This includes research performed by NIH directly.

Introduction

(1) Experiments in which recombinant DNA[1] is introduced into cells of a human subject with the intent of stably modifying the subject's genome are covered by Section III-A-4 of the NIH Guidelines for Research Involving Recombinant DNA Molecules (49 Federal Register 46266). Section III-A-4 requires such experiments to be reviewed by the NIH Recombinant DNA Advisory Committee (RAC) and approved by the NIH. RAC consideration of each proposal will be on a case-by-case basis and will follow publication of a precis of the proposal in the Federal Register, an opportunity for public comment, and a review of the proposal by the working group of the RAC. RAC recommendations on each proposal will be forwarded to the NIH Director for a decision which will then be published in the Federal Register. In accordance with Section IV-C-1-b of the NIH Guidelines, the NIH Director may approve proposals only if he finds that they present "no significant risk to health or the environment."

(2) In general, it is expected that somatic-cell gene therapy protocols will not present a risk to the environment as the recombinant DNA is expected to be confined to the human subject. Nevertheless, Section I-B-4-b of the "Points to Consider" document asks the researchers to address specifically this point.

[1]Section III-A-4 applies both to recombinant DNA and to DNA or RNA derived from recombinant DNA.

(3) This document is intended to provide guidance in preparing proposals for NIH consideration under Section III-A-4 of the NIH Guidelines for Research Involving Recombinant DNA Molecules. Not every point mentioned in the "Points to Consider" document will necessarily require attention in every proposal. The document will be considered for revision as experience in evaluating proposals accumulates and as new scientific developments occur. This review will be carried out at least annually.

(4) A proposal will be considered by the RAC only after the protocol has been approved by the local Institutional Biosafety Committee (IBC) and by the local Institutional Review Board (IRB) in accordance with Department of Health and Human Services (DHHS) Regulations for the Protection of Human Subjects (45 Code of Federal Regulations, Part 46). If a proposal involves children, special attention should be paid to subpart D of these DHHS regulations. The IRB and IBC may, at their discretion, condition their approval on further specific deliberation by the RAC and its working group. Consideration of gene therapy proposals by the RAC may proceed simultaneously with review by any other involved federal agencies[2] provided that the RAC is notified of the simultaneous review. Meetings of the committee will be open to the public except where trade secrets or proprietary information would be disclosed. The committee would prefer that the first proposals submitted for RAC review contain no proprietary information or trade secrets, enabling all aspects of the review to be open to the public. The public review of these protocols will serve to inform the

[2]The Food and Drug Administration (FDA) has jurisdiction over drug products intended for use in clinical trials of human somatic-cell gene therapy. For general information on FDA's policies and regulatory requirements, please see the Federal Register, Volume 51, pages 23309-23313, 1986.

public not only on the technical aspects of the proposals but also on the meaning and significance of the research.

(5) The clinical application of recombinant DNA techniques to human gene therapy raises two general kinds of questions: (1) the questions usually discussed by IRBs in their review of any proposed research involving human subjects; and (2) broader social issues. The first type of question is addressed principally in Part I of this document. Several of the broader social issues surrounding human gene therapy are discussed later in this Introduction and in Part II below.

(6) Following the Introduction, this document is divided into four parts. Part I deals with the short-term risks and benefits of the proposed research to the patient[3] and to other people, as well as with issues of fairness in the selection of patients, informed consent, and privacy and confidentiality. In Part II, investigators are requested to address special issues pertaining to the free flow of information about clinical trials of gene therapy. These issues lie outside the usual purview of IRBs and reflect general public concerns about biomedical research. Part III summarizes other requested documentation that will assist the RAC and its working group in their review of gene therapy proposals. Part IV specifies reporting requirements.

(7) A distinction should be drawn between making genetic changes in somatic cells and in germ line cells. The purpose of somatic cell gene therapy is to treat an individual patient, e.g., by inserting a properly functioning

[3]The term "patient" and its variants are used in the text as a shorthand designation for "patient-subject."

gene into a patient's bone marrow cells in vitro and then reintroducing the cells into the patient's body. In germ line alterations, a specific attempt is made to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring. The RAC and its working group will not at present entertain proposals for germ line alterations but will consider for approval protocols involving somatic-cell gene therapy.

(8) The acceptability of human somatic-cell gene therapy has been addressed in several recent public documents as well as in numerous academic studies. The November 1982 report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Splicing Life, resulted from a two-year process of public deliberations and hearings; upon release of that report, a House subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, Human Gene Therapy, which brought these earlier documents up-to-date. As the latter report concluded:

> "Civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies."

(9) Concurring with this judgment, the RAC and its working group are prepared to consider for approval somatic-cell therapy protocols, provided that the design of such experiments offers adequate assurance that their consequences will not go beyond their purpose, which is the same as the traditional purpose of all clinical investigations, namely, to benefit the health and well-being of the individual being treated while at the same time gathering generalizable knowledge.

(10) Two possible undesirable consequences of somatic-cell therapy would be unintentional (1) vertical transmission of genetic changes from an individual to his or her offspring or (2) horizontal transmission of viral infection to other persons with whom the individual comes in contact. Accordingly, this document requests information that will enable the RAC and its working group to assess the likelihood that the proposed somatic-cell gene therapy will inadvertently affect reproductive cells or lead to infection of other people (e.g., treatment personnel or relatives).

(11) In recognition of the social concern that surrounds the general discussion of human gene therapy, the working group will continue to consider the possible long-range effects of applying knowledge gained from these and related experiments. While research in molecular biology could lead to the development of techniques for germ line intervention or for the use of genetic means to enhance human capabilities rather than to correct defects in patients, the working group does not believe that these effects will follow immediately or inevitably from experiments with somatic-cell gene therapy. The working group will cooperate with other groups in assessing the possible long-term consequences of somatic-cell gene therapy

and related laboratory and animal experiments in order to define appropriate human applications of this emerging technology.

(12) Responses to the questions raised in these "Points to Consider" should be provided in the form of either written answers or references to specific sections of the protocol or its appendices.

I. Description of Proposal

A. Objectives and rationale of the proposed research

State concisely the overall objectives and rationale of the proposed study. Please provide information on the following specific points:

1. Why is the disease selected for treatment by means of gene therapy a good candidate for such treatment?

2. Describe the natural history and range of expression of the disease selected for treatment. What objective and/or quantitative measures of disease activity are available? In your view, are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene therapy?

3. Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims?

4. What alternative therapies exist? In what groups of patients are these therapies effective? What are their relative advantages and disadvantages as compared with the proposed gene therapy?

B. Research design, anticipated risks and benefits

1. Structure and characteristics of the biological system

Provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following are specific points to be addressed:

a. What is the structure of the cloned DNA that will be used?

(1) Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme map of the total construct.

(2) What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)?

(3) Describe the steps used to derive the DNA construct.

b. What is the structure of the material that will be administered to the patient?

(1) Describe the preparation, structure, and composition of the materials that will be given to the patient or used to treat the patient's cells.

(a) If DNA, what is the purity (both in terms of being a single DNA species and in terms of other contaminants)?

What tests have been used and what is the sensitivity of the tests?

(b) If a virus, how is it prepared from the DNA construct? In what cell is the virus grown (any special features)? What medium and serum are used? How is the virus purified? What is its structure and purity? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (for example, VL30 RNA, other nucleic acids, or proteins) or contaminating viruses or other organisms in the cells or serum used for preparation of the virus stock?

(c) If co-cultivation is employed, what kinds of cells are being used for co-cultivation? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials? Specifically, what tests are being done to assess the material to be returned to the patient for the presence of live or killed donor cells or other non-vector materials (for example, VL30 sequences) originating from those cells?

(d) If methods other than those covered by (a)-(c) are used to introduce new genetic information into target cells, what steps are being taken to detect and eliminate any

contaminating materials? What are possible sources of contamination? What is the sensitivity of tests used to monitor contamination?

(2) Describe any other material to be used in preparation of the material to be administered to the patient. For example, if a viral vector is proposed, what is the nature of the helper virus or cell line? If carrier particles are to be used, what is the nature of these?

2. Preclinical studies, including risk-assessment studies

Describe the experimental basis (derived from tests in cultured cells and animals) for claims about the efficacy and safety of the proposed system for gene delivery.

a. Laboratory studies of the delivery system

(1) What cells are the intended recipients of gene therapy? If recipient cells are to be treated in vitro and returned to the patient, how will the cells be characterized before and after treatment? What is the theoretical and practical basis for assuming that only the treated cells will act as recipients?

(2) Is the delivery system efficient? What percentage of the target cells contain the added DNA?

(3) How is the structure of the added DNA sequences monitored and what is the sensitivity of the analysis? Is the added

DNA extrachromosomal or integrated? Is the added DNA unrearranged?

(4) How many copies are present per cell? How stable is the added DNA both in terms of its continued presence and its structural stability?

b. Laboratory studies of gene expression

Is the added gene expressed? To what extent is expression only from the desired gene (and not from the surrounding DNA)? In what percentage of cells does expression from the added DNA occur? Is the product biologically active? What percentage of normal activity results from the inserted gene? Is the gene expressed in cells other than the target cells? If so, to what extent?

c. Laboratory studies pertaining to the safety of the delivery/expression system

(1) If a retroviral system is used:

(a) What cell types have been infected with the retroviral vector preparation? Which cells, if any, produce infectious particles?

(b) How stable are the retroviral vector and the resulting provirus against loss, rearrangement, recombination, or mutation? What information is available on how much rearrangement or recombination with endogenous or other

viral sequences is likely to occur in the patient's cells? What steps have been taken in designing the vector to minimize instability or variation? What laboratory studies have been performed to check for stability, and what is the sensitivity of the analyses?

(c) What laboratory evidence is available concerning potential harmful effects of the treatment, e.g., development of neoplasia, harmful mutations, regeneration of infectious particles, or immune responses? What steps have been taken in designing the vector to minimize pathogenicity? What laboratory studies have been performed to check for pathogenicity, and what is the sensitivity of the analyses?

(d) Is there evidence from animal studies that vector DNA has entered untreated cells, particularly germ line cells? What is the sensitivity of the analyses?

(e) Has a protocol similar to the one proposed for a clinical trial been carried out in non-human primates and/or other animals? What were the results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?

(2) *If a non-retroviral delivery system is used:* What animal studies have been done to determine if there are pathological

or other undesirable consequences of the protocol (including insertion of DNA into cells other than those treated, particularly germ line cells)? How long have the animals been studied after treatment? What tests have been used and what is their sensitivity?

3. Clinical procedures, including patient monitoring

Describe the treatment that will be administered to patients and the diagnostic methods that will be used to monitor the success or failure of the treatment. If previous clinical studies using similar methods have been performed by yourself or others, indicate their relevance to the proposed study.

a. Will cells (e.g., bone marrow cells) be removed from patients and treated *in vitro* in preparation for gene therapy? If so, what kinds of cells will be removed from the patients, how many, how often, and at what intervals?

b. Will patients be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy) prior to gene therapy?

c. What treated cells (or vector/DNA combination) will be given to patients in the attempt to administer gene therapy? How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple treatments? If so, over what period of time?

d. What are the clinical endpoints of the study? Are there objective and quantitative measurements to assess the natural history of the disease? Will such measurements be used in following your patients? How will patients be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses? How frequently will follow-up studies be done? How long will patient follow-up continue?

e. What are the major potential beneficial and adverse effects of treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of potential adverse effects on patients with the probability and magnitude of deleterious consequences from the disease if gene therapy is not performed.

f. If a treated patient dies, what special studies will be performed as part of the autopsy?

4. Public-health considerations

Describe any potential benefits and hazards of the proposed therapy to persons other than the patients being treated. Specifically:

a. On what basis are potential public health benefits or hazards postulated?

b. Is there a significant likelihood that the added DNA will spread from the patient to other persons or to the environment?

c. What precautions will be taken against such spread (e.g., to patients sharing a room, health-care workers, or family members)?

d. What measures will be undertaken to mitigate the risks, if any, to public health?

5. Qualifications of investigators, adequacy of laboratory and clinical facilities

Indicate the relevant training and experience of the personnel who will be involved in the preclinical studies and clinical administration of gene therapy. In addition, please describe the laboratory and clinical facilities where the proposed study will be performed.

a. What professional personnel (medical and nonmedical) will be involved in the proposed study? What are their specific qualifications and experience with respect to the disease to be treated and with respect to the techniques employed in molecular biology? Please provide curricula vitae (see Section III-E).

b. At what hospital or clinic will the treatment be given? Which facilities of the hospital or clinic will be especially important for the proposed study? Will patients occupy regular hospital beds or clinical research center beds? Where will patients reside during the follow-up period?

C. Selection of patients

Estimate the number of patients to be involved in the proposed study of gene therapy. Describe recruitment procedures and patient eligibility

requirements, paying particular attention to whether these procedures and requirements are fair and equitable.

1. How many patients do you plan to involve in the proposed study?

2. How many eligible patients do you anticipate being able to identify each year?

3. What recruitment procedures do you plan to use?

4. What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

5. How will patients be selected if it is not possible to include all who desire to participate?

D. Informed consent

Indicate how patients will be informed about the proposed study and how their consent will be solicited. The consent procedure should adhere to the requirements of DHHS regulations for the protection of human subjects (45 Code of Federal Regulations, Part 46). If the study involves pediatric or mentally handicapped patients, describe procedures for seeking the permission of parents or guardians and, where applicable, the assent of each patient. Areas of special concern highlighted below include potential adverse effects, financial costs, privacy, and long-term follow-up.

1. How will the major points covered in Sections I-A through I-C of this document be disclosed to potential participants in this study

and/or parents or guardians in language that is understandable to them?

2. How will the innovative character and the theoretically-possible adverse effects of gene therapy be discussed with patients and/or parents or guardians? How will the potential adverse effects be compared with the consequences of the disease? What will be said to convey that some of these adverse effects, if they occur, could be irreversible?

3. What explanation of the financial costs of gene therapy and any available alternative therapies will be provided to patients and/or parents or guardians?

4. How will patients and/or their parents or guardians be informed that the innovative character of gene therapy may lead to great interest by the media in the research and in treated patients?

5. How will patients and/or their parents or guardians be informed:

   a. That some of the procedures performed in the study may be irreversible?

   b. That following the performance of such procedures it would not be medically advisable for patients to withdraw from the study?

   c. That a willingness to cooperate in long-term follow-up (for at least three to five years) will be a precondition for participation in the study?

d. That a willingness to permit an autopsy to be performed in the event of a patient's death following treatment is also a precondition for a patient's participation in the study? (This stipulation is included because an accurate determination of the precise cause of a patient's death would be of vital importance to all future gene therapy patients.)

E. Privacy and confidentiality

Indicate what measures will be taken to protect the privacy of gene therapy patients and their families as well as to maintain the confidentiality of research data.

1. What provisions will be made to honor the wishes of individual patients (and the parents or guardians of pediatric or mentally handicapped patients) as to whether, when, or how the identity of patients is publicly disclosed?

2. What provision will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients?

II. Special Issues

Although the following issues are beyond the normal purview of local IRBs, the RAC and its working group request that investigators respond to questions A and B below.

A. What steps will be taken, consistent with point I-E above, to ensure that accurate information is made available to the public with respect to such public concerns as may arise from the proposed study?

B. Do you or your funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in the proposed study? If so, what steps will be taken to permit as full communication as possible among investigators and clinicians concerning research methods and results?

III. Requested Documentation

In addition to responses to the questions raised in these "Points to Consider," please submit the following materials:

A. Your protocol as approved by your local IRB and IBC. The consent form, which must have IRB approval, should be submitted to the NIH only on request.

B. Local IRB and IBC minutes and recommendations that pertain to your protocol.

C. A one-page scientific abstract of the gene therapy protocol.

D. A one-page description of the proposed experiment in nontechnical language.

E. Curricula vitae for professional personnel.

F. An indication of other federal agencies to which the protocol is being submitted for review.

G. Any other material which you believe will aid in the review.

IV. Reporting Requirements

A. Serious adverse effects of treatment should be reported immediately to both your local IRB and the NIH Office for Protection from Research Risks, and a written report should be filed with both groups. A copy of the report should also be forwarded to the NIH Office of Recombinant DNA Activities (ORDA).

B. Reports regarding the general progress of patients should be filed at six-month intervals with both your local IRB and ORDA. These twice-yearly reports should continue for a sufficient period of time to allow observation of all major effects (at least three to five years). In the event of a patient's death, the autopsy report should be submitted to the IRB and ORDA.